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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,165	07/26/2002	Paul B. Fisher	34585-A-PCT/USA070050.166	4970

21003 7590 08/18/2005

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,165	FISHER ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7-25-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7-25-05 has been entered.

Claims 1-8 and 10-19 have been canceled. Claim 9 is pending and under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 9 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 9 is directed to a mouse comprising a transgene comprising a nucleic acid encoding a reverse tetracycline controlled transactivator protein under the control of EF-1 alpha promoter.

The claim reads on any mouse comprising a nucleic acid encoding a reverse tetracycline controlled transactivator protein under the control of EF-1 alpha promoter. The claim encompasses chimeric mice and transgenic mice comprising the transgenic in its genome with

unknown and unidentified phenotypes. The specification teaches making a transgenic mouse via microinjection of pEF1prtTA vector into pronuclei of fertilized mouse eggs and implanted said fertilized eggs into pseudo-pregnant female mice. The specification discloses the establishment of a female founder mouse and the F1 generation, and 8 out of 15 F1 generation mice were tested positive for the transgene (see specification, p. 20-21).

The specification fails to disclose the structural features or phenotypes of the claimed chimeric mice or transgenic mice. The specification fails to provide adequate guidance and evidence for the production of and how to use various chimeric mice and heterozygous or homozygous transgenic mice, which have their phenotypes that are distinguishable from corresponding wild type mice. The specification also fails to provide adequate guidance and evidence for how to use a chimeric mouse or a transgenic mouse having no phenotype or phenotype indistinguishable from wild type mice.

The state of the art of transgenics at the time of the invention held that the phenotype of transgenic mice was unpredictable. Leonard et al., 1995 (Immunological Reviews, Vol. 148, pages 97-114) disclosed mice with a disruption in the gc gene that was intended to be a model for X-linked severe combined immunodefkiency (XSCID), but display a variety of unexpected traits (abstract). Kappel et al., 1992 (Current Opinion in Biotechnology, Vol. 3, p. 548-553) reports that the individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct, the site of integration, etc., are the important factors that governs the expression of a transgene (e.g. p. 549)). Sigmund, C., June 2000 (Arterioscler. Thromb. Vasc. Biol., p. 1425-1429), reports that variation in the genetic background contributes to unpredictable resulting phenotypes of transgenic or gene-targeted animals. "Animals

containing the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype" (e.g. abstract). Sigmund further states that "many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studies...Although all mouse strains contain the same collection of genes, it is allelic variation...and the interaction between allelic variants that influence a particular phenotype. These "epigenetic" effects can dramatically alter the observed phenotype and therefore can influence or alter the conclusions drawn from experiments" (e.g. introduction). The resulting phenotype of a transgenic mouse was unpredictable at the time of the invention.

In addition, the specification only discloses the presence of the transgene DNA in the founder and F1 generation of transgenic mice but fails to provide evidence for the expression pattern of the transgene in the claimed transgenic mice and whether the transgene expression could be stimulated by the presence of inducer, such as tetracycline, within the claimed transgenic mice. The specification also fails to provide adequate guidance and evidence for whether the expressed reverse tetracycline controlled transactivator protein can stimulate the expression of a gene of interest in a double transgenic mouse comprising a gene of interest under the control of Tc-operator. Absent the evidences set forth above, one skilled in the art at the time of the invention would not know how to use the claimed transgenic mice in making a double transgenic mouse expressing a gene of interest in which said double transgenic mouse shows a particular phenotype(s) distinguishable from the wild type mouse.

As discussed above, the claim reads on chimeric mice. The specification fails to enable making chimeric mice such that they exhibit any phenotype, including a wild-type phenotype. The method of making genetic mosaic mice is such that each resulting chimera is comprised of a different, unpredictable ratio of cells of various genotypes. This ratio cannot be predetermined. Furthermore, the spatial distribution of cells of each genotype cannot be predetermined. Therefore, the phenotype of chimeric mice is not only dependent upon the genotype of the cells (which is unpredictable as set forth by the state of the art outlined above, for example see Leonard; Sigmund) but is also dependent upon the spatial distribution of the cells and their relative population size. Thus, the phenotype of the chimeric mice encompassed by the claims is highly unpredictable. The specification fails to provide the guidance necessary to overcome this high level of unpredictability to generate a chimeric mouse exhibiting any specific phenotype or any phenotype other than wild type. Absent a predictable phenotype, one skilled in the art would require trial and error experimentation to determine a useful phenotype for the claimed transgenic mice or chimeric mice and trial and error experimentation to determine how to use said transgenic mice and chimeric mice. Therefore, without undue experimentation, one skilled in the art would not know how to use the transgenic mice and chimeric mice encompassed by the claim.

In view of the inherent unpredictability of the resulting phenotypes of the claimed transgenic mice and chimeric mice and the lack of evidence for the phenotypes of the claimed transgenic mice and the chimeric mice, one skilled in the art at the time of the invention would not know how to use the claimed mouse without phenotypes or with phenotype indistinguishable from wild type mice.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of ordinary skill which is high, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Applicants argue that some issued patents have claims directed to transgenic mice having no disclosed phenotype and one of ordinary skill in the art could predictably generate a transgenic mouse expressing a second gene of interest regardless of the resulting phenotype of that mouse. Applicants further argue that the specification teaches how to prepare transgenic expression cassette and how to make and use transgenic mice (amendment, p. 6-8). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph rejection and the following reasons.

Firstly, each patent deals with different type of transgenic mouse and has to be considered individually. US Patent No. 5,922,927 cited by applicants provides the expression pattern of the tTA transgene in the claimed transgenic mice and suppression of the tTA transgene expression when the transgenic mice are exposed to tetracycline. However, the specification of the instant invention fails to provide evidence for the expression pattern of the transgene (rtTA) in the claimed transgenic mice and whether the transgene expression could be stimulated by the presence of inducer, such as tetracycline, within the claimed transgenic mice. The specification also fails to provide adequate guidance and evidence for whether the expressed reverse tetracycline controlled transactivator protein can stimulate the expression of a gene of interest in

a double transgenic mouse comprising a gene of interest under the control of Tc-operator. Thus, one skilled in the art at the time of the invention would not know how to use the claimed transgenic mice in making a double transgenic mouse expressing a gene of interest in which said double transgenic mouse shows a particular phenotype(s) distinguishable from the wild type mouse.

Secondly, although the method of preparing expression cassette and making transgenic mice were known in the art, however, the resulting phenotype of the transgenic mice and chimeric mice was unpredictable at the time of the invention. Absent the phenotype of the transgenic mice or chimeric mice, one skilled in the art at the time of the invention would not know how to use the claimed mice and would require undue experimentation to determine a useful phenotype of the claimed mice or to determine how to use the claimed mice to make a transgenic mice having a useful phenotype.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Shin-Lin Chen, Ph.D.